REMARKS

Claims 1-27 are pending and under examination in the above-identified application. Claims 1, 2, 8, 9, 10, 18 and 19 have been amended above. Support for the amendments can be found throughout the application. Specifically, support for the amendment to claims 1, 2, 8 and 9 can be found, for example, at paragraph 0018 and in claim 19 as originally filed. Support for the amendment to claim 10 can be found, for example, at paragraph 0018. Support for the amendment to claim 19 can be found, for example, at paragraph 0012 and in claim 1 as originally filed. The amendment to claim 18 merely corrects the dependency of that claim to base claim 10. Accordingly, the amendments do not raise an issue of new matter and entry thereof is respectfully requested. Applicant has reviewed the rejections set forth in the Office Action mailed August 26, 2003, and respectfully traverse all grounds for the reasons that follow.

Rejections Under 35 U.S.C. § 101

Claims 10-18 stand rejected under 35 U.S.C. § 101 for lacking utility allegedly because the invention is inoperative. In this regard, the Office asserts that neurons are terminally differentiated cells and are incapable of proliferating. The Office concludes that there is no evidence of record to suggest that transfection of a neuron with a vector containing a growth factor would induce a neuron to proliferate.

Applicant submits that claims 10-18 are operative as filed. For example, the application describes at, for example, paragraph 0018, that the vectors of the invention have the ability "to regulate neuronal differentiation and survival during development of the nervous system and also in the adult state." Further, paragraph 0018 further teaches that the vectors of the invention can be expected to "facilitate control of adult neurons with regard to maintenance, functional performance, and aging of normal cells; repair and regeneration processes in chemically or mechanically lesioned cells; and prevention of degeneration and premature death." Accordingly, these descriptions teach the method of claim 10 as filed.

Nevertheless, to further prosecution of the instant application, Applicant has amended claim 10 above to recite a method for enhancing the survival of a nerve cell. The application teaches enhancing survival of a nerve cell at, for example, paragraph 0018 wherein it describes that the vectors of the invention are applicable to "enhance survival of neurons and other neuronal cells in both the central nervous system and the peripheral nervous system. Accordingly, the rejection under 35 U.S.C. § 101 is rendered moot and its withdrawal is respectfully requested.

Rejections Under 35 U.S.C. § 112

Claims 19-27 stand rejected under 35 U.S.C. § 112, first paragraph, for allegedly lacking enablement. The Office concedes that the claimed invention is enabled for promoting survival in humans of: (1) entorhinal layer II neurons by intrahippocampal injection of a viral vector encoding an anti-apoptotic gene of the Bcl-2 family; (2) nigral-TH positive neurons by intrastriatal injection of a viral vector encoding an anti-apoptotic gene of the Bcl-2 family, or (3) spinal motorneurons by intramuscular injection of viral vector encoding insulin-like growth factor-1, where the encoded genes are expressed. However, the Office asserts the specification fails to enable the full scope of the claimed invention allegedly because the claims do not require that the therapeutic gene be expressed in the target neuron, and because *in vivo* gene therapy was unpredictable and an undeveloped art at the time the invention was made.

With respect to the first assertion, Applicant contends that expression of the claimed therapeutic gene is an inherent outcome of the claimed method of transduction. For example, the application teaches:

> Embodiments of the invention involve delivery of a substantially non-toxic, recombinant adeno-associated virus vector having a heterologous gene of interest in order to provide retrograde gene delivery with *stable gene expression.*

Page 6, paragraph 0012 (emphasis added).

At various places elsewhere throughout the application, the invention is described as a targeted delivery strategy for transduction and retrograde gene delivery for gene therapy of a

therapeutic product. However, to further prosecution of this application, Applicant has amended claim 19 above to recite that the therapeutic gene is expressed. Accordingly, this ground of rejection is rendered moot and Applicant respectfully requests its withdrawal.

With respect to the assertion that the claimed invention lacks predictability, the Office cites Orkin et al. (1995), alleging that the conclusions drawn in that report apply to the claimed invention. Verma et al. (1997) is cited in further support of Orkin et al., allegedly describing that gene therapy protocols lack efficient gene delivery and sustained expression. Rosenberg et al. (2000) is cited allegedly for describing that gene therapy lacks clinical efficacy and Hsich et al. (2002) is cited allegedly for describing that gene therapy for neurological diseases include unique difficulties and that very few protocols for peripheral diseases have shown any degree of success. The Office concludes that because Hsich et al. raise apparent concerns at a time after the invention was made it is a clear indication that knowledge in the art was lacking for successful gene therapy of neurological diseases.

Orkin et al. (1995) is a NIH committee report on gene therapy procedures published in 1995, which was six years earlier than the filing date of the instant application. The purpose of the committee was to "to assess the current status and promise of gene therapy and provide recommendations regarding future NIH-sponsored research in this area." (page 1, first paragraph). The report appears to discuss various aspects of gene therapy research and NIH funding recommendations. However, the report does not describe any pitfalls associated with viral transduction and retrograde transport as claimed by the current invention. In fact, the report fails to even mention viral transduction and retrograde transport at all. Because Orkin et al. was published six years prior to the filing date of the instant application and because it fails to consider the claimed method, this reference is inapplicable to support the alleged lack of enablement of the claimed invention.

Similarly, Verma et al. (1997) is a publication that appears to summarize certain aspects of gene therapy procedures as of its 1997 publication date, which was four years earlier than the filing date of the instant application. Verma et al. appears to be directed to gene

delivery procedures and describes different vectors and methods used for this purpose in gene therapy procedures. However, similar to Orkin et al., Verma et al. also fails to address viral transduction and retrograde transport of viral vectors as is claimed by the current invention. Therefore, Verma et al. also is inapplicable to support the allegation that the claimed method lacks enablement.

The citation of Rosenberg et al. (2000) also is similarly inapplicable to support the alleged lack of enablement of the claimed invention. As with Orkin et al. and Verma et al., Rosenberg et al. was published prior to the filing date of the instant application and also fails to describe viral transduction of neurons and retrograde transport of the viral vector. Accordingly, Rosenberg et al. fails to support the rejection of claims 19-27 for lack of enablement.

Hsich et al. (2002) is purported to describe that very few protocols for peripheral diseases have shown any degree of success. However, Hsich et al. does not describe any significant deficiencies associated with viral transduction and retrograde transport as claimed in the application. In fact, Hsich et al. actually reports positive results with retrograde transport when it describes:

> A number of common human pathogenic viruses, for example, Ad, HSV, adeno-associated virus (AAV), and retrovirus have been used as vectors by taking advantage of their natural propensity to insert genetic material into target cell nuclei (Tables 3 and 4). Typically, capsid/virions can be transported long distances in the brain through retrograde transport within neuronal processes, and HSV and lentivirs are known to establish quiescent, stable infection in the CNS. Synthetic vectors, which can include delivery components and DNA elements from a variety of sources, have great promise for optimizing gene delivery.

Page 583, col. 2, last paragraph. Therefore, Hsich et al. describes the successful use of viral vectors and retrograde transport and additionally describes that this method is a promising candidate for further optimization. There is nothing in this description to distract from the use of this general approach for targeted gene delivery as is currently claimed by the invention.

Because neither Orkin et al. (1995), Verma et al. (1997), Rosenberg et al. (2000) or Hsich et al. (2002) describe deficiencies associated with viral transduction and retrograde gene delivery as claimed by the invention, any negative treatment of gene therapy protocols by these references is non-analogous and inapplicable to the claimed invention. Accordingly, these references fail to support the alleged lack of enablement of the claimed invention.

With respect to the asserted lack of enablement for the full scope of the invention, the Office further alleges that: (1) although the results described in the specification show retrograde transport specificity for some neurons, the ability of an AAV viral vector to transfect a particular neuron is required to be determined empirically; (2) the specification fails to teach target neurons, location of their terminal field or suitable therapeutic genes for neurodegenerative diseases other than Alzheimer's disease, Parkinson's disease or ALS, and (3) the specification fails to identify a target disease, target neuron or the location of the terminal field of target neurons where the recited glutamate receptors, FGF, NT-3, BDNF and GDNF genes would be used. Ozawa et al. is cited for allegedly describing that retrograde transport is generally restricted to a gene product rather than vector. Simon et al. is cited for allegedly describing that transfection of retinal ganglion cells with an AAV vector carrying a bcl-2 gene led to greater susceptibility to apoptosis, allegedly supporting that bcl-2 therapy cannot be predicted for all neurons. Finiels et al. is cited for allegedly describing that transfection of motor neurons with an AAV vector expressing NT-3 extended the life of an animal model for ALS, but that GDNF, CTNF, BDNF or combinations thereof had no effect on survival. Based on the above, the Office concludes that the protective effect of specific neurotrophic factors on specific neurons lacks predictability and that the detail required to comply with the enablement requirement is more than a minor omission of information that is well known in the art.

To be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. The specification must provide a reasonable number of species and guidance sufficient to teach those skilled in the art how to make and use the invention as claimed. *Genentech, Inc. v. Novo Nodisk A/S*, 108 F.3d 1361, 1365, 42 U.S.P.Q.2d 1001, 1004 (Fed. Cir. 1997), *see also* MPEP

§2164.01(c), fourth paragraph. Further, in *Johns Hopkins Univ. v. CellPro, Inc.*, 152 F.3d 1342, 1360 (Fed. Cir. 1998), the Federal Circuit clearly stated that routine experimentation does not constitute undue experimentation:

> The test [for undue experimentation] is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention claimed.

Id. (*citing PPG Indus., Inc. v. Guardian Indus. Corp.*, 75 F.3d 1558, 1564 (Fed. Cir. 1996); *see also In re Wands*, 858 F.2d 731, 736-40 (Fed. Cir. 1988)).

The application as filed complies with this standard. Claim 19 is directed to a method for treating a neurodegenerative disease. The method includes introducing a viral vector containing a therapeutic gene into a terminal field of target neurons of a patient under conditions that result in transduction of the viral vector into the synaptic end, migration to the cellular end of the target neurons and expression of the therapeutic gene. The application provides sufficient teachings and guidance to enable the full scope of this claim.

As conceded by the Office, the application enables at least three different embodiments of the claimed method. First, the application enables the claimed method for promoting the survival in humans of entorhinal layer II neurons by intrahippocampal injection of a viral vector encoding an anti-apoptotic gene of the Bcl-2 family. This specific example is described, for example, at pages 20-21 of the application as filed. Second, the application enables the claimed method for promoting the survival in humans of nigral-TH positive neurons by intrastriatal injection of a viral vector encoding an anti-apoptotic gene of the Bcl-2 family (pages 21-22, for example). Third, as stated in the Office Action, the application enables the claimed method for promoting spinal motorneurons by intramuscular injection of viral vector encoding insulin-like growth factor-1 (page 22, for example).

These specific examples enable use of the claimed method for the treatment of at least three neurodegenerative diseases, namely, Alzheimer's Disease (p.20 for example),

Parkinson's Disease (p.21, for example) and Amyotrophic Lateral Sclerosis (ALS; p.22, for example). These specific examples further enable the use of at least two different therapeutic genes, a Bcl-2 family member and insulin-like growth factor I, in the claimed method. Further, these specific examples enable the use of the claimed method for viral transduction and retrograde delivery to three different sites, namely, intrahippocampal, intrastriatal and intrastriatal, having three different target neurons and three different terminal fields. These teachings of the claimed method in such diverse applications provide a sufficient number of species and guidance to enable the full scope of invention as claimed. Further, the application provides a broad range of additional teachings and guidance sufficient to teach those skilled in the art how to make and use the invention as claimed for neurodegenerative diseases other than those exemplified above.

With respect to the Office's assertion regarding retrograde transport specificity, target neurons and associated diseases and applicable therapeutic genes, Applicant respectfully points out that the application provides substantial teachings and guidance for how to make and use the invention without undue experimentation. For example, in addition to the specific descriptions above exemplifying the claimed method, the application describes how to make and test targeted retrograde transport of transduced vectors. In this regard, the application describes, for example, at page 13, exemplary methods for producing viral vectors. At pages 13-16, the application describes, for example, exemplary methods for introducing and testing retrograde transport of viral vectors and expression of a reporter gene. These pages also describe a method for confirming the specificity of viral vector for target neurons. The application further describes an alternative method for confirming infection of viral particles using fluorescent markers at, for example, pages 16-17. Pages 17-18, for example, describe an exemplary method for confirming active transcription of a reporter gene transduced into projection neurons. Pages 18-19, for example, describe exemplary methods for confirming the expression of a reporter gene in spinal cord neurons. Accordingly, these descriptions teach both how to make and use the invention and how to confirm successful application of the claimed methods to a particular disease, target neuron or use of a therapeutic gene.

Further, the application describes at, for example, pages 20-23, additional specific uses of the claimed method of the invention. In addition the application describes a sufficient range of diseases, target neurons and therapeutic genes applicable to the claimed method of the invention. These teachings and guidance throughout the application sufficiently enable how to make and use the claimed invention without undue experimentation. These descriptions teach a reasonable number of specific examples and provide a reasonable amount of guidance with respect to how to practice a desired embodiment. Accordingly, any descriptions in Ozawa et al., Simon et al. and Finiels et al. allegedly supporting unpredictability of the claimed invention fails to adequately refute or outweigh the express teachings of the application and the guidance in the application for how to practice a particular embodiment of the claimed invention. Therefore, the application teaches how to make and use the full scope of the claimed invention without undue experimentation. *Genentech,* 108 F.3d at 1365; *Johns Hopkins Univ.,* 152 F.3d at 1360; *PPG Indus.,* 75 F.3d at 1564; *In re Wands*, 858 F.2d at 736-40. In light of the above remarks, Applicant respectfully requests that the rejection of claims 19-27 under 35 U.S.C. § 112, first paragraph be withdrawn.

Claims 12 and 17 also stands rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite for use of the phrase "incubating said nerve cell under conditions" in claim 12, and for use of the phrase "a nerve growth factor" in claim 17. In this regard, the Office alleges that the term "incubate" in the context of a cell means to maintain the cell in a medium under controlled environmental conditions. The Office analogizes this purported meaning to cell culture.

Applicant respectfully submits that the term "incubate" includes maintaining something such as a cell or chemical reaction under controlled conditions. However, the term as it is understood in the art does not exclude *in vivo* incubation. For example, the first entry in Webster's dictionary for the term "incubate" refers to hatching eggs via the warmth of the body (attached as Exhibit A). *Webster's Third New International Dictionary, Unabridged.* Merriam-Webster, 2002. http://unabridged.merriam-webster.com (27 Apr. 2004) (*see also* first two entries for term "incubating"). Further, the definition for the term "incubating" expressly includes

controlled *in vivo* conditions when it defines the term to mean "the period between the infection of a plant or animal by a pathogen and the manifestation of the disease it causes" (attached as Exhibit B). *Webster's Third New International Dictionary, Unabridged.* Merriam-Webster, 2002. http://unabridged.merriam-webster.com (27 Apr. 2004). Accordingly, the use of the term "incubating" in claim 12 is clear to those skilled in the art based on its ordinary meaning. Therefore, Applicant respectfully requests that this ground of rejection be withdrawn.

With respect to the use of the phrase "a nerve growth factor" in claim 17, the Office asserts that nerve growth factor or NGF is a specific trophic factor that does not include IGF-1. The Office asserts that it is unclear what the term "nerve growth factor" refers to in claim 17 since claim 18 recites that the nerve growth factor of claim 17 is IGF-1, but that the application describes that IGF-1 is an alternative.

Applicant respectfully submits that page 22 of the application describes use of nerve growth factor or IGF-1 in the claimed methods to treat ALS or spinal injury. This description is exemplary of factors that can be used in the claimed method of the invention. Further, there is nothing in this description that teaches the use of one factor at the exclusion of the other factor. However, to further prosecution, Applicant has amended claim 18 to depend from claim 10. Accordingly, this ground of rejection is moot and is respectfully requested to be withdrawn.

Rejections Under 35 U.S.C. § 102

Claims 1-4, 8 and 9 stand rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Senut et al. The Office asserts Senut et al. describe the injection of infectious particles of AAV-GFP or AAV-97Q-GFP into the striatum of rats and observed the expression of the gene products in the substantia nigra and ventral tegmental area consistent with retrograde transport of the vectors. The Office asserts that, although Senut et al. could not distinguish between transport of the gene product or the vector, retrograde transport of the vector is

presumed because, absent evidence to the contrary, the instant application describes that transduced viral vectors are transported in such a manner.

Applicant submits that the claims as filed are distinct from the method described in Senut et al. However, to further prosecution of the instant application, claim 1 has been amended to recite that the claimed method is directed to transducing a human neuron. Senut et al. appears to describe the use of viral vectors encoding the reporter gene GFP for expression in rats. Because Senut et al. is directed to reporter gene expression in rats, this reference cannot anticipate the invention of claims 1-4, 8 and 9. Accordingly, Applicant respectfully request that this ground of rejection be withdrawn.

Claims 1-4, 8 and 9 also stand rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Peterson et al. The Office asserts that Peterson et al. describe the injection of AAV vectors expressing a GFP/Bcl-xL fusion protein into the hippocampus, resulting in transfection and protection of ECL2 neurons by retrograde transport.

Applicant submits that the claims as filed are distinct from the method described in Peterson et al. In this regard, Peterson et al. is an abstract that appears to summarize preliminary results of injecting viral vectors into rats. Without conceding that this abstract constitutes an enabling disclosure, Peterson et al. fail to describe transduction of human neurons. Therefore, Peterson et al. cannot anticipate the invention of claims 1-4, 8 and 9 and Applicant respectfully requests that this ground of rejection be withdrawn.

Claims 1-9 stand rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Bartlett et al. The Office asserts that Bartlett et al. describe the intrahippocampal injection of vector particles of an AAV vector expressing GFP into rats. Xiao et al. is supplied allegedly for supporting that the injected dose is about $2.5x10^8$ infectious particles. The Office asserts that retrograde transport of the vector must have inherently occurred because the experiment described by Bartlett et al. is essentially the same as the description at pages 13-16 in the instant application.

Applicant submits that the claims as filed are distinct from the method described in Bartlett et al. Moreover, Applicant does not concede that the experiment described by Bartlett et al. is essentially the same as the description at pages 13-16 of the instant application. Further, Bartlett et al. fail to describe transduction of human neurons as is currently claimed. Therefore, Bartlett et al. cannot anticipate the invention of claims 1-4, 8 and 9 and withdrawal of this ground of rejection is respectfully requested.

Claims 1, 2, 4-7, 19, 20 and 22-25 stand rejected under 35 U.S.C. § 102(e) as allegedly anticipated by Horellou et al., US 2002/0031493. The Office asserts Horellou et al. describe a method of treating Parkinson's disease by intrastriatal injection of an adenoviral vector containing a therapeutic gene encoding GDNF in a rat model. Transfection of substantia nigra is asserted to have occurred via retrograde transport.

Applicant submits that the claims as filed are distinct from the method described in Horellou et al. Moreover, Applicant does not concede that the studies described by Horellou et al. are essentially the same as the invention described the application. As stated previously, to further prosecution, Applicant has amended claim 1 to recite the transduction of human neurons. Horellou et al. fail to describe the transduction of human neurons. Therefore, Horellou et al. cannot anticipate the invention of claims 1, 2, 4-7, 19, 20 and 22-25 and withdrawal of this ground of rejection is respectfully requested.

Claims 1, 2, 4-7, 19, 20 and 22-25 stand rejected under 35 U.S.C. § 102(e) as allegedly anticipated by Finiels et al., US 6,632,427. The Office asserts that Finiels et al. describe a method for treating ALS by intramuscular injection of an adenoviral vector expression NT-3 via retrograde transport in SOD mice. The Office notes that a substantially higher vector dose would be required to treat humans compared to the $5\text{-}10^9$ pfu used in Finiels.

As with the previous rejections under 35 U.S.C. § 102, Finiels et al. fail to describe methods for the transduction of human neurons. Accordingly, Finiels et al. cannot

anticipate the invention of claims 1, 2, 4-7, 19, 20 and 22-25 and withdrawal of this ground of rejection is respectfully requested.

Rejections Under 35 U.S.C. § 103

Claims 19-21 and 25-27 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over Peterson et al. The Office asserts Peterson et al. describe the injection of AAV vectors expressing a GFP/Bcl-xL fusion protein into the hippocampus, resulting in transfection and protection of ECL2 neurons by retrograde transport. The Office further asserts that Peterson et al. describe that AAV vectors can be used to deliver therapeutic transgenes in animal models of Alzheimer's disease. The Office concludes that Peterson et al. provides a reasonable expectation of success for protecting neuron degeneration in human because the rat used is a model protecting entorhinal neurons in Alzhimer's patients.

Claim 19 is directed to a method for treating a neurodegenerative disease. The method consists of introducing a viral vector containing a therapeutic gene into a terminal field of target neurons of a patient under conditions that result in transduction of the viral vector into the synaptic end, migration to the cellular end of the target neurons and expression of the therapeutic gene. Peterson et al. fail to teach or suggest the claimed invention with a reasonable expectation of success. At most, Peterson et al. might be considered an invitation to experiment.

Peterson et al. appear to describe that hippocampal neurons were found to be infected at the site of injection and further purports to describe a capacity for retrograde transport of "virus and/or protein" from the dentate gyrus to ECL2. The purpose of the study described by Peterson et al. is to "evaluate" the therapeutic potential of anti-apoptotic genes and, in this context, Peterson et al. conclude that the "data indicate that rAAV can be used to deliver therapeutic transgenes in *an animal model* of Alzheimer's disease. (Emphasis added).

Because the purpose of the study was to evaluate the therapeutic potential of certain genes, but the conclusion was expressly restricted to an animal model, Peterson et al. cannot suggest the use of the described method in humans with a reasonable expectation of success. If Peterson et al. believed that the reported results indicated a therapeutic potential in

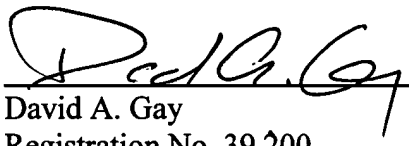
humans, Peterson et al. would have said so because of the direct relationship between the purpose of the study and human gene therapy. Moreover, Peterson et al. also raise uncertainties whether expression occurred due to retrograde transport of the protein or of the virus. These descriptions fail to provide more than a plan of research. Accordingly, Peterson et al. does not teach or suggest all elements of the claimed invention with a reasonable expectation of success. Therefore, withdrawal of this ground of rejection is respectfully requested.

CONCLUSION

In light of the Amendments and Remarks herein, Applicant submits that the claims are in condition for allowance and respectfully request a notice to this effect. Should the Examiner have any questions, he is invited to call the undersigned attorney.

Respectfully submitted,

Date: April 30, 2004



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